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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/713,970 | 11/14/2003 | Roland Contreras | 17106 | 5158 |
| 23389 7590 05/23/2007 SCULLY SCOTT MURPHY & PRESSER, PC 400 GARDEN CITY PLAZA SUITE 300 GARDEN CITY, NY 11530 | | | EXAMINER GEBREYESUS, KAGNEW H | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/713,970

Applicant(s)

CONTRERAS ET AL.

Examiner

Kagnew H. Gebreyesus

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 January 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4 and 10-38 is/are pending in the application.
- 4a) Of the above claim(s) 28-38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 10-27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response on January 22, 2007 to the Office Action dated August 1, 2006 is acknowledged. Applicants have cancelled claims 5-9, claims 1, 10, 13, 15, 18, 20, 23, 24-26 are currently amended. Claims 1-4, 10-27 are present for examination.

Objection - Oath/Declaration

The oath or declaration remains defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: It does not identify the mailing address of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

Withdrawn - Claim Rejections - 35 USC § 112

Claims 1-4 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is withdrawn because Applicants have amended the claims by incorporating limitations that define the genetic modification in the microorganism.

Maintained - Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 10-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue: "...Applicants observe that previous claim 5 is not included in the rejection. As submitted above, Applicants have amended claim 1 to incorporate the features of previous claims 5-6. Present claim 1 specifically delineates the genetic modifications contained in the strain. Applicants have also amended claim 1 to delete the characterization of the mammalian-like N-glycan as containing five or fewer mannose residues. Applicants respectfully submit that the presently claimed subject matter is adequately described in the specification. Accordingly, Applicants respectfully submit that the written description rejection under 35 U.S.C. § 112, first paragraph, is overcome..."

However previous claim 5 also included the limitation in previous claim 2 wherein the methanotrophic yeast strain comprises the mammalian-like-N-glycan structure, GalGlcNAcMan₅GlcNAc₂. Claim 1 as amended does not include the limitation of previous claim 2. Thus the yeast strain in claim 1 comprises any N-glycan structure including N-glycans with five or more mannoses or structures with three mannose residues which require the presence of additional enzymes such as mannosidase II that removes two mannose residues from GalGlcNAcMan₅GlcNAc₂.

In this case, the specification discloses a genetically engineered yeast strain that produces a glycoprotein comprising a single representative species of a mammalian-like-N-glycan structure, GalGlcNAcMan₅GlcNAc₂. However, the specification fails to describe genetically engineered yeast strain(s) that produce glycoproteins comprising any other species of mammalian-like N-glycan structures by any identifying characteristics or property other than the specific N-glycan comprising GalGlcNAcMan₅GlcNAc₂ produced using the specific enzymes recited in claim 1. Such disclosure would require disclosure of the enzymes that make the genus of mammalian N-glycan structures since the yeast strain must "express" them.

While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

In the instant case the recited yeast strains are claimed to produce a genus of mammalian-like N-glycans, thus encompasses species widely variant with respect to their structures. However, Applicants have not described any other yeast strains wherein other enzymes are expressed or disrupted in view of obtaining a strain that produces any mammalian N-glycan. Thus the description of a single yeast strain wherein a single species of a mammalian N-glycan structure (GalGlcNAcMan₅GlcNAc₂) in which three enzymes (alpha-1,2-mannosidase, N-acetylglucosaminyltransferase I and a beta-1,4-galactosaminyltransferase or functional parts thereof) are expressed is insufficient to provide description for yeast strain that produce a genus of mammalian

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like N-glycans structures claimed in claim 1 because applicants have not provided description for any additional modifying enzymes which must be expressed or disrupted.

As such, the disclosure of the single species of modified yeast strain glycoprotein is insufficient to be representative of the attributes and features of all species encompassed by the claimed genus.

Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim 1-4, 10-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a yeast strain genetically engineered to produce the specific mammalian-like N-glycan structure consisting of GalGlcNAcMan5GlcNAc2, does not reasonably provide enablement for a genetically engineered strain that produce a glycoprotein comprising any mammalian-like N-glycan structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants argue:

"...Applicants respectfully submit that the foregoing amendments to the claims have adequately addressed the Examiner's rejection. Specifically, present claim 1 delineates the genetic modifications contained in the strain. Claim 1, as amended, also does not include the characterization of "five or fewer mannose residues" particularly objected to by the Examiner. Applicants respectfully submit that the presently claimed subject matter is fully supported by the specification, and is also consistent with the scope

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acknowledged by the Examiner as enabled. Accordingly, Applicants respectfully submit that the enablement description rejection under 35 U.S.C. § 112, first paragraph, is overcome. Withdrawal of the rejection is respectfully requested..."

However the rejection under 35 U.S.C. 112, first paragraph based on the recitation of "...five or fewer residues..." is because the specification does not teach a strain that produces any representative N-glycan other than GalGlcNAcMan₅GlcNAc₂. Amended claim 1 now encompasses a scope that is even broader than the original claim because the claim now encompasses N-glycan structures comprising 3 mannose residues which can be further modified to produce other mammalian like N-glycans. However as previously explained the specification only provides guidance and an example for a genetically engineered methylotrophic yeast stain, *Pichia pastoris* wherein the OCH1 gene was disrupted thus preventing high mannosylation and wherein an α -1, 2-mannosidase, N-acetylglucosaminyltransferase I (or GnTI), and a β -1, 4-galactosyltransferase (GalT) are expressed. Said strain produces a glycoprotein comprising a specific mammalian-like-N-glycan structure, namely GalGlcNAcMan₅GlcNAc₂. The specification does not teach genetic modifications required to produce a strain that produces any mammalian-like-N-glycan structure as encompasses in claim 1.

Factors to be considered in determining whether undue experimentation is required, are summarized in *re Wands* (858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)). The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill

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of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The standard for meeting the enablement requirement is whether one of skill in the art can make the invention without undue experimentation. The amount of experimentation to make the claimed invention is enormous and undue. Such experimentation entails expressing additional enzymes such as mannosidase II, fucosyltransferases, sialyltransferases (which further modify N-glycans) because yeast do not naturally express enzymes required for the production of mammalian-like N-glycans or disrupting enzymes such as Mnn6p and Mnn1p (involved in mannosylation in yeast) to reduce hypermannosylation of core glycans.

However Applicants have not provided sufficient guidance or working examples that can enable the scope encompassed by the claims.

The nature and breadth of the claims encompass any yeast strain that produces a glycoprotein comprising any mammalian-like N-glycan structure.

However the specification does not teach how the genetically engineered *Pichia pastoris* strain comprising the specific enzymes α -1, 2-mannosidase, N-acetylglucosaminyltransferase I (or GnTI) or a functional part thereof, and a β -1, 4-galactosyltransferase (GalT) or a functional part thereof in which the OCH1 gene is disrupted and wherein said strain can produce any glycoprotein comprising any mammalian-like N-glycan structure using any working example.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific enzymes required to be expressed or

disrupted, in order to produce a strain that produces a glycoprotein comprising any mammalian-like N-glycan structure. Without such guidance, the experimentation left to those skilled in the art is undue.

Withdrawn - Claim Rejections - 35 USC § 102

Claims 1-27 as they apply to claims 1-4, 10-27 were rejected under 35 U.S.C. 102(e) as being anticipated by Gerngross et al. Applicant's argument has been carefully considered and was found persuasive. Therefore the rejection under 35 U.S.C. 102(e) as being anticipated by Gerngross et al is withdrawn.

Closest prior art:

Gerngross et al (US 7029872 B2): Teaches use of *Pichia pastoris* with a disrupted α -1, 6-mannosyltransferase (OCH1) gene, which is further transformed with human α -1, 2-mannosidase, and at least two enzymes selected from N-acetylglucosamine transferase I (GnT1), (GnT I-VI), mannosidase II, fucosyltransferase, galactosyl transferase (GalT) or sialyltransferases (ST) in view of producing modified glycosylation pathways in eukaryotic cells in particular in *Pichia pastoris*. While Gerngross et al teach a general strategy for producing a genus of strains suitable for the production of glycoproteins comprising a genus of mammalian-like N-glycans, they do not disclose the specific strain disclosed by the instant invention because Applicants use *Trichoderma Reesei* α -1, 2-mannosidase, instead of human α -1, 2-mannosidase used by Gerengross et al. More specifically Gerengross et al use human α -1, 2-mannosidase that functions with a PH optimum of 6.0 as opposed to the *Trichoderma Reesei* α -1, 2-mannosidase has an optimum PH of 5.0. Thus Applicant's disclosure is a species of a non-preferred embodiment from the broader genus of Gerengross et al's disclosure.

Contreras, Roland et al. US 20020188109 A1: Teach use of *Pichia pastoris* with a disrupted α -1, 6-mannosyltransferase (OCH1) gene, which is further transformed with human α -1, 2-mannosidase, and glucosidase II.

This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an

appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal from, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kagnaw H. Gebreyesus whose telephone number is 571-272-2937. The examiner can normally be reached on 8:30am-5: 30pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Examiner: Kagnev Gebreyesus PhD.
May 18, 2007
KHG


KATHLEEN KERR BRAGDON, PH.D.
SUPERVISORY PATENT EXAMINER